US006083208A

United States Patent [19]

Modak et al.

[11] Patent Number: 6,083,208

[45] Date of Patent: *Jul. 4, 2000

[54] **TRICLOSAN-CONTAINING MEDICAL DEVICES**

[75] Inventors: **Shanta Modak**, River Edge, N.J.; **Sampath Lester**, Nyack, N.Y.

[73] Assignee: **The Trustees of Columbia University of the City of New York**, New York, N.Y.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **09/062,411**

[22] Filed: **Apr. 17, 1998**

Related U.S. Application Data

[63] Continuation of application No. 08/583,239, Jan. 5, 1996, Pat. No. 5,772,640.

[51] **Int. Cl.**[7] **A61M 25/00**

[52] **U.S. Cl.** **604/265**; 424/422; 623/1; 428/35.7

[58] **Field of Search** 604/264–265; 606/76; 428/35.7–36.9; 424/422; 623/1

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,605,564	8/1986	Kulla et al. .
4,723,950	2/1988	Lee .
4,994,047	2/1991	Walker et al. .
5,019,096	5/1991	Fox, Jr. et al. .
5,033,488	7/1991	Curtis et al. .
5,091,442	2/1992	Milner .
5,102,401	4/1992	Lambert et al. .
5,165,952	11/1992	Soloman et al. .
5,180,605	1/1993	Milner .
5,200,194	4/1993	Edgren et al. .
5,209,251	5/1993	Curtis et al. .
5,261,421	11/1993	Milner .
5,335,373	8/1994	Dangman et al. .
5,772,640	6/1998	Modak et al. .

FOREIGN PATENT DOCUMENTS

9302717	2/1993	WIPO .

OTHER PUBLICATIONS

The Merck Index, An Encyclopedia of Chemicals, Drugs, and Biologicals, Tenth Edition (Merck & Co., Inc. Rahway, NJ, 1983), p. 1092.

Primary Examiner—Mark Bockelman
Attorney, Agent, or Firm—Baker Botts L.L.P.

[57] **ABSTRACT**

The present invention relates to polymeric medical articles comprising the antiinfective agents chlorhexidine and triclosan. It is based, at least in part, on the discovery that the synergistic relationship between these compounds permits the use of relatively low levels of both agents, and on the discovery that effective antimicrobial activity may be achieved when these compounds are comprised in either hydrophilic or hydrophobic polymers.

16 Claims, No Drawings

relatively high amounts of antiinfective agent. The following impregnating solutions comprised chlorhexidine, triclosan and either Silastic Type A, polycaprolactone, or no polymer in a 5% methanol/95% THF solvent. Table XV shows that when both polymer and antiinfective agent were comprised in the impregnating solution, higher antiinfective activity was achieved.

TABLE XV

Impregnating Solution	Zone Of Inhibition (mm)
4% SilA + 5% CHA + 1% TC	12.0
1% polycaprolactone + 5% CHA + 1% TC	12.0
No polymer, 5% CHA + 1% TC	6.5

13. EXAMPLE

Diffusion of Antiinfective Agents From Medical Articles Treated With Impregnating Solutions With and Without Polymer

The following impregnating solutions, "A" and "B", were used to impregnate segments of Dacron and PTFE grafts. The treated grafts were then rinsed with saline, and the amounts of antiinfective agent incorporated into the grafts were determined, before and after rinsing, by extraction of antiinfective agent with dichloromethane/methanol/water (50%/25%/25%, v/v). The results, set forth in Table XVI, demonstrate that the addition of a polymer to the impregnating solution produces a treated medical article which exhibits greater retention of antiinfective agent.

Solution A:	1% polycaprolactone + 0.1% CHA + 0.02% TC, in 5% methanol/95% THF (v/v)
Solution B:	0.1% CHA + 0.02% TC, in 5% methanol/95% THF (v/v)

TABLE XVI

	Drug Levels (μg/cm)			
	Dacron Graft		PTFE Graft	
Solution:	A	B	A	B
Solution A				
Before rinsing	392	548	73	90
After rinsing	353	547	56	88
Solution B				
Before Rinsing	409	573	50	44
After rinsing	132	553	24	44

14. EXAMPLE

Drug Uptake and Release by Hydrophilic Catheters Impregnated With Chlorhexidine or Triclosan

Polyurethane central venous catheter segments fabricated of Tecoflex 93-A polyurethane were impregnated with solutions "C", "D", "E", "F" and "G" set forth below by soaking the catheter segments for about two minutes followed by drying and rinsing with water. Drug uptake was measured by extracting the impregnated catheter segments with dichloromethane/methanol/water (50%/25%/25% v/v). Drug release was measured over a period of six days by suspending the catheter segments in saline (one 2 cm segment in 2 ml saline), and agitated in a heated water bath at 37° C.; the saline was changed daily and drug release was measured as described above. The results are shown in Table XVII. Polyurethane, as set forth below, is Tecoflex 93-A polyurethane.

Solution C:	3% polyurethane + 3% CHA in 30% reagent alcohol/70% THF
Solution D:	3% polyurethane + 3% TC in 30% reagent alcohol/70% THF
Solution E:	3% polyurethane + 2% CHA + 2% TC, in 30% reagent alcohol/70% THF
Solution F:	2% CHA in 95% ethanol
Solution G:	3% CHA + 1% TC in 95% ethanol

TABLE XVII

Solution	Drug	Uptake (μg/cm)	Drug Release (μg/cm) Day No. 1	2	3	4	5	6
C	CHA	197	78	36	20	2.6	0.8	0.8
D	TC	300	0.4	.13	0.1	0.1	0.1	0.1
E	CHA	202	66	16.8	7.0	5.0	5.0	5.0
	TC	230	0.4	0.3	<.1	<.1	<.1	<.1
F	CHA	254	15	9.6	7.8	2.5	2.5	2.5
G	CHA	223	7.1	3.5	3.0	0.8	0.8	0.8
	TC	368	<.1	<.1	<.1	<.1	<.1	<.1

15. EXAMPLE

Release of Chlorhexidine and Triclosan From Impregnated Silicone Catheter Segments

Segments of silicone central venous catheters fabricated from Dow Corning Q7-4765A silicone polymer or Q7-4765B silicone polymer were impregnated with either solution H or I by soaking for 30 minutes, and then the release of drug was measured daily by methods set forth above. The results of these measurements are presented in Table XVIII.

Solution H: 2% SilA+5% CHA in 10% methanol/90% THF (v/v)

Solution I: 2% SilA+5% CHA+2% TC in 10% methanol/90% THF (v/v)

TABLE XVIII

Solution	Drug	Daily Release (μg/cm) Day 1	Day 2	Day 3	Day 4	Day 5
H	CHA	2.7	1.0	0.6	0.9	0.9
I	CHA	0.8	0.9	0.6	0.8	0.8
	TC	2.6	5.6	2.3	1.5	1.5

Various publications are cited herein, which are hereby incorporated by reference in their entireties.

What is claimed is:

1. A hydrophilic polymeric medical article having a coating resulting from dipping or soaking the article in a treatment solution comprising between about 2 and 6 percent by weight of a biomedical polyurethane; between 0.5 and 2 percent by weight of triclosan; between 0.5 and 1 percent by weight of silver sulfadiazine; and between 1.5

and 2 percent by weight of an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative.

2. The medical article of claim 1 which is a catheter.

3. The catheter of claim 2 which is an intravenous catheter.

4. The catheter of claim 3 which is fabricated from a biomedical polyurethane.

5. The catheter of claim 4 wherein the hydrophilic polymer in the coating is a biomedical polyurethane.

6. A hydrophobic polymeric medical article treated with a treatment solution comprising between about 1 and 10 percent by weight of a silicone polymer; between 0.5 and 2 percent by weight of triclosan; and between 1.5 and 2.25 percent by weight of an antiinfective agent selected from the group consisting of chlorhexidine free base, a chlorhexidine salt, and a chlorhexidine derivative.

7. The medical article of claim 6, further comprising silver sulfadiazine.

8. The medical article of claim 7 wherein the medical article is fabricated from a hydrophobic polymer selected from the group consisting of polyvinylchloride, polytetrafluoroethylene, Dacron and a silicone polyurethane copolymer.

9. The medical article of claim 7 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

10. The medical article of claim 7 wherein the medical article is fabricated from a silicone polymer.

11. The medical article of claim 6 wherein the medical article is fabricated from a hydrophobic polymer selected from the group consisting of polytetrafluoroethylene, Dacron, polyvinylchloride and a silicone polyurethane copolymer.

12. The medical article of claim 6 wherein the medical article is fabricated from a silicone polymer.

13. The medical article of claim 6 wherein the hydrophobic polymer in the treatment solution is a silicone-polyurethane copolymer.

14. The medical article of claim 6 which is a catheter.

15. The catheter of claim 14 which is an intravenous catheter.

16. The catheter of claim 15 which is fabricated from a biomedical silicone polymer.

* * * * *